I. PEPTIDERGIC CONTROL OF CIRCADIAN TIMING: ROLE OF VASOACTIVE INTESTINAL PEPTIDE (VIP), PEPTIDE HISTIDINE ISOLEUCINE (PHI)AND GASTRIN RELEASING PEPTIDE (GRP).

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The suprachiasmatic nucleus (SCN) appears to function as a circadian clock that times rhythms in nearly all behavioral and physiological endpoints. Although there is a wealth of anatomical data indicating that neurons within the SCN contain high levels of a variety of neuropeptides, comparatively little is known about how these peptides contribute to biological timekeeping. VIP, PHI and GRP are found in a large percentage of SCN neurons that receive direct synaptic input from the afferent pathways that appear to be responsible for synchronizing the circadian clock in the SCN with the 24-hr day-night cycle. Since VIP and PHI are consistently co-localized in neurons within the SCN and at least some neurons contain VIP, PHI and GRP, we have examined how the corelease of these peptides may regulate circadian timing. Previously, we have shown that microinjection of a cocktail containing equimolar concentrations of VIP, PHI and GRP into the SCN produce delays in the timing of circadian rhythms that mimic the delays produced by exposure to pulses of light. These data suggest that VIP, PHI and GRP interact to influence the clock mechanism within the SCN or act on other neurochemical signals that in turn affect the clock. One neurochemical signal that may interact with VIP, PHI and GRP to influence circadian timing is GABA. Recent data indicate that GABA is found in all or nearly all SCN neurons. To determine if GABA influences the phase shifting effects of VIP/PHI/GRP within the SCN, VIP/PHI/GRP was coadministered with the $GABA_A$ agonist, muscimol, or the $GABA_A$ antagonist, bicuculline. Coadministration of VIP/PHI/GRP with muscimol significantly reduced the phase delaying effects of the peptides, and coadministration of VIP/PHI/GRP with bicuculline significantly increased the phase delaying effects of the peptides. These data support the hypothesis that VIP/PHI/GRP phase shift circadian rhythms by interacting with a $GABA_A$ dependent mechanism in the SCN.

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